REMARKS

Claims 1-21 are pending. In the instant amendments, claims 9, 12 and 17-19 have been canceled without prejudice. Claims 1-5, 11 and 13-16 have been amended. Upon entry of the claim amendments, claims 1-8, 10-11, 13-16 and 20-21 will be pending and under consideration.

Amendments to the Claims

Claims 1-5 have been amended to delete non-elected subject matter. Applicants reserve the right to pursue the canceled subject matter in one or more continuation or divisional applications.

Claim 11 have been amended to delete the term "prevention."

Claims 11 and 15 have been amended to recite "HIV infection." Support for this amendment is found, for example, in original claims 11 and 15, and at page 3 of the specification.

Claim 13 has been amended to recite a method of treating of preventing an inflammatory or immunoregulatory disorder or disease comprising administering a compound of claim 1 or its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof. Support for this amendment is found, for example, in original claims 12-13 and in the specification at pages 1-3.

Claims 14-16 have been amended to depend from claim 13.

These amendments are fully supported by the specification and claims as filed. No new matter is added by the amendments. Entry of the above amendments is respectively requested.

Claim Objections

The Examiner has objected to claims 1-11 and 20 as allegedly containing non-elected subject matter. (Office Action, page 2). As mentioned above, claims 1-5 have been amended to delete non-elected subject matter. Upon entry of the claim amendments, claims 6-11 and 20, which depend from claim 1, do not contain non-elected subject matter. Therefore, Applicants respectfully request that the claim objections be withdrawn.

Claim Rejections under 35 U.S.C. § 112

The Examiner has rejected claims 9-10, 12-19 and 21 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. (Office Action, page 2). Specifically, the Examiner alleges that, while the claims are enabled for the treatment of asthma and granulomas, the specification "does not reasonably provide enablement for the simultaneous treatment and prevention of diseases and disorders related to CCR3, treatment or prevention of all disorders related to CCR3, and the prevention of asthma." (Office Action, page 2). Applicants respectfully disagree.

Factors to be considered in determining whether a disclosure meets the enablement requirement have been set forth in *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir 1988). They include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability in the art, (4) the presence or absence of working examples, (5) the amount of guidance presented, (6) the breadth of the claims, (7) the quantity of experimentation necessary, and (8) the level of skill in the art. The initial burden is on the Office to provide evidence of non-enablement for each of these factors. *See In re Wands*, 8 U.S.P.Q.2d at 1404; MPEP §§ 2164.01(a); 2164.04 (emphasis provided).

Claims 10-11 and 13-15 recite specific classes of diseases and disorders associated with the CCR3 receptor, as disclosed in the specification at pages 1-3. Specifically, the instant claims recite the treatment of inflammatory, immunoregulatory and allergic diseases, and more specifically, asthma, rhinitis, autoimmune pathologies, HIV, lung granuloma, and Alzheimer's disease. The instant specification teaches that compounds that antagonize CCR3 are useful in treating these specific diseases and disorders. (*See* pages 1-3). The specification provides many examples of compounds that antagonize the CCR3 receptor. (*See* pages 40-68). Therefore, one of ordinary skill in the art, reading the instant specification at the time of the invention, would have been able to practice the full scope of the instant claims without undue experimentation. To support this conclusion, each *Wands* factor is addressed in detail below.

1. The nature of the invention.

The Examiner states that the instant invention is drawn to methods of inhibiting the CCR3 receptor with the compounds recited in the instant claims. (Office Action, page 3). Applicants first point out that claims 9, 12 and 17-19, directed to compositions and methods for treating CCR3 related diseases and disorders generally, have been canceled. Thus, the

invention is drawn to the compounds and compositions of claims 1-8 and 10-11, and methods of using these compounds to treat a limited number of specific classes of diseases associated with the CCR3 receptor– inflammatory, immunoregulatory and allergic diseases.

2. The breadth of the claims.

Applicants again point out that claims 12 and 17-19, directed to methods of treating CCR3 related diseases and disorders generally, have been canceled. Thus, the presently amended method claims recite specific classes of diseases and disorders associated with CCR3, and one of ordinary skill in the art, reading the instant disclosure, would be able to determine which specific diseases or disorders are within these classes of disease. Furthermore, CCR3 was known at the time of the invention to have an active role in these classes of disease. (*See* pages 1-3 of the specification, and the references cited and discussed below). Indeed, specific examples of these diseases are disclosed in the application and in the relevant art. Therefore, in view of the teachings of the instant disclosure, the instant claims are not overly broad.

3. The state of the prior art.

The Examiner acknowledges, citing Ponath (*Expert Opinion on Investigational Drugs*, 1998, 7(1): 1-18) and Bertrand *et al.* (*Expert Opinion on Investigational Drugs*, 2000, 9(1): 43-52) that CCR3 is linked to the treatment of asthma and granulomas. (Office Action, page 3). Applicants point out that, in addition to asthma and granulomas, CCR3 was well known in the art to be linked to inflammatory, immunoregulatory and allergic diseases at the time of the invention. Therefore, one skilled in the art, at the time of the invention, would have expected the compounds of the instant claims, which are CCR3 antagonists, to be effective in the treatment of the diseases and disorders of the instant claims.

a. Asthma, rhinitis and allergic diseases

Claims 10 and 14 recite compositions and methods of treating asthma, rhinitis, allergic diseases, and autoimmune pathologies with the compounds of claim 1. The compounds of claim 1 are CCR3 antagonists. Applicants point out that it was well known at the time of the invention that allergic diseases, including rhinitis, are associated with the CCR3 receptor. Pages 1-2 of the instant specification teach that CCR3 was known at the time of the invention to have an active role in eosinophil-related diseases– diseases that include allergic disorders such as rhinitis. Indeed, the Examiner himself points out that

CCR3 was known at the time of the invention to be associated with asthma. (Office Action, page 3).

To further identify the state of the art at the time of the invention, Applicants point to White *et al.*, "Identification of potent, selective, non-peptide CC chemokine receptor-3 antagonist that inhibits eotaxin-, eotaxin-2-, and monocyte chemotactic protein-4-induced eosinophil migration," *J. Bio. Chem.*, Vol. 275, No. 47, pp. 36626-31 (2000) ("White," copy enclosed with Information Disclosure Statement). White teaches that non-peptide CCR3 antagonists inhibit human eosinophil chemotaxis in response to certain natural CCR3 ligands. (*Id.* at 36629). Based on this discovery, White encourages those skilled in the art to develop non-peptide CCR3 antagonists as therapeutic agents for eosinophil-related diseases including allergic diseases such asthma, allergic rhinitis, atopic dermatitis and eosinophilic gastroenteritis. (*Id.* at 36626 and 36629). The compounds of the instant claims are non-peptide CCR3 antagonists, therefore, White demonstrates that one of ordinary skill in the art at the time of the invention would have expected the CCR3 antagonists of the instant claims to be useful in treating allergic rhinitis and other allergic diseases and disorders.

Based on the teachings of the instant specification and the above references, the state of the art at the time of the invention was such that one of ordinary skill in the art would expect a CCR3 antagonist to have potential as a therapeutic agent against allergic diseases such as asthma and rhinitis. Thus, the instant claims are enabled, to the extent they teach the treatment of asthma, rhinitis and other allergic diseases, for the reasons stated above.

b. Autoimmune pathologies

Claims 10 and 14 recite compositions and methods of treating asthma, rhinitis, allergic diseases, and autoimmune pathologies with the compounds of claim 1. The specification lists rheumatoid arthritis, Grave's disease, and atherosclerosis as examples of autoimmune pathologies (*See* page 2, line 35). Autoimmune pathologies such as rheumatoid arthritis, Grave's disease, and atherosclerosis were known in the art at the time of the invention to be associated with CCR3 activity. (*See* specification, page 2; Katschke *et al.*, "Differential Expression of Chemokine Receptors on Peripheral Blood, Synovial Fluid, and Synovial Tissue Monocytes/Macrophages in Rheumatoid Arthritis," *Arthritis & Rheumatism*, Vol. 44, No. 5, pp. 1022-32 (2001) ("Katschke," copy provided in the enclosed Information Disclosure Statement); Haley *et al.*, "Overexpression of Eotaxin and the CCR3 Receptor in Human Atherosclerosis: Using Genomic Technology to Identify a Potential Novel Pathway of Vascular Inflammation," *Circulation*, Vol. 102, pp. 2185-89 (2000) ("Haley," copy

provided in the enclosed Information Disclosure Statement); Simchen *et al.* "Expression and Regulation of Regulated on Activation, Normal T Cells Expressed and Secreted in Thyroid Tissue of Patients with Graves' Disease and Thyroid Autonomy and in Thyroid-Derived Cell Populations," *J. Clinical Endocrinology & Metabolism*, Vol. 85, No. 2, 4758-64 (2000) ("Simchen," copy provided in the enclosed Information Disclosure Statement)).

For example, Katschke demonstrates that monocytes of the blood and synovial fluid from the joints of patients with rheumatoid arthritis showed significantly more expressed CCR3 when compared to normal joints. (Katschke, page 1022). Katschke concludes that CCR3 is a "potential therapeutic target" for rheumatoid arthritis because treatment of rheumatoid arthritis patients with "specific agents that deplete CCR3+ ... cells may be effective in intervening in the chronic inflammatory process." Thus, CCR3 was implicated in rheumatoid arthritis at the time of the invention.

CCR3 overexpression had also been shown in osteoarthritic human tissue at the time of the invention. For example, Alaaeddine *et al.* demonstrate that CCR3 receptors were overexpressed in osteoarthritic human cartilage take from human patients. "Production of the Chemokine RANTES by Articular Chrondrocytes and Role in Cartilage Degradation," *Arthritis & Rheumatism*, Vol. 44, No. 7, pp. 1633-43 (2001) ("Alaaeddine," copy provided in the enclosed Information Disclosure Statement). Alaaeddine further teaches that several chemokines, including those that bind CCR3, "have been implicated in the pathogenesis of arthritis" generally, and that there is "strong support for the role of chemokines" in rheumatoid arthritis. (*Id.* at 1639-40). Thus, as shown above, CCR3 was known to be associated with both rheumatoid and osteoarthritis the time of the invention.

Simchen teaches that the thyroid glands of Graves' disease patients have substantially elevated levels of lymphocytes, including T cells having CCR3 receptors. (Simchen, page 4758). These T cells expressed RANTES, a natural ligand of CCR3, in significantly higher amounts than that of the peripheral bloodstream. (*Id.*). Simchen concluded that this overexpression of RANTES may be involved in the autoimmune response in Graves' disease. (*Id.*). Therefore, it was known in the art at the time of the invention that the CCR3 receptor was implicated in Graves' disease.

Haley teaches that CCR3 is overexpressed in human tissue from atherosclerotic arteries. (Haley, page 2185). Normal arterial samples showed negligible CCR expression, leading the authors to conclude that CCR3 is an interesting target for the treatment of atherosclerosis. (*Id.* at 2185 and 2189). Thus, CCR3 was known to be associated with

atherosclerosis at the time of the invention. One of ordinary skill in the art would expect that, based on the teachings of Alaaeddine and Haley, CCR3 antagonism would be an attractive method for the treatment of atherosclerosis.

As demonstrated above, CCR3 overexpression was known to be common in many types of autoimmune pathologies. Therefore, the state of the art at the time of the invention was such that one of ordinary skill would have expected CCR3 antagonism to be a promising means for treating autoimmune pathologies. Thus, the instant claims are enabled, to the extent they teach the treatment of autoimmune pathologies, for the reasons stated above.

c. HIV infection

Claims 11 and 15 recite, *inter alia*, compositions and methods for the treatment of HIV infection. At the time of the invention, it was known in the art that CCR3 was associated with HIV infection. *See, e.g.,* Marone *et al.*, "Are Mast Cells MASTers in HIV-1 Infection?," *Int. Arch. Allergy Immunol.*, Vol. 125, pp. 89-95 (2001) ("Marone," cited in the specification at page 3, copy provided in enclosed Information Disclosure Statement); Li *et al.*, "Mast Cells/Basophils in the Peripheral Blood of Allergic Individuals Who Are HIV-1 Susceptible Due to Their Surface Expression of CD4 and the Chemokine Receptors CCR3, CCR5 and CXCR4," *Blood*, Vol. 97, No. 11, pp. 3484-87 (2001) ("Li," cited in the specification at page 3, copy provided in enclosed Information Disclosure Statement).

Marone and Li teach that mast cells and basophils are targets of HIV infection though the virus' interaction with the CCR3 receptor, which is expressed on the cellular surface. (Marone, page 91-92, Li, page 3484). Li further teaches that mast cells and basophils are susceptible to a specific strain of HIV because the cells express chemokines such as CCR3. (Li, page 3485). It was also known at the time of the invention that alveolar macrophages, another important type of host-defense cells that express CCR3, were targeted by HIV-1. Park *et al.*, "CD4 Receptor-Dependent Entry of Human Immunodeficiency Virus Type-1 *env*-Pseudotypes into CCR5-, CCR3- and CXCR4-Expressing Human Alveolar Macrophages Is Preferentially Mediated by the CCR5 Coreceptor," *Am. J. Respir. Cell Mol. Biol.*, Vol. 20, pp.864-871 (1999) ("Park," copy provided in enclosed Information Disclosure Statement). Park teaches that the entry of a specific pseudotype of HIV into alveolar macrophages was mediated by CCR3 or CCR5. (Park, page 864). These references demonstrate that CCR3 was known to be associated with HIV infection of a number of different cells through multiple pathways of infection. Based on the above teachings, one of ordinary skill in the art at the time of the invention would expect that the compounds of the instant claims, which

inhibit CCR3, would be useful in treating HIV infection. Therefore, claims 11 and 15 are enabled to the extent that they teach compositions and methods for the treatment of HIV infection.

d. Alzheimer's disease

Claims 11 and 15 recite, *inter alia*, compositions and methods for the treatment of Alzheimer's disease. Alzheimer's disease was known in the art at the time of the invention to be associated with chemokines such as CCR3. *See, e.g.,* Xia *et al.*, "Immunohistochemical Study of the β–Chemokine Receptors of CCR3 and CCR5 and Their Ligands in Normal and Alzheimer's Diseases Brains," *Am. J. Pathology*, Vol. 153, No. 1, pp. 31-36 (1998) ("Xia I", cited in the specification at page 3, copy provided with the enclosed Information Disclosure Statement). Specifically, it was known in the art that chemokine receptors, including CCR3, were expressed on the surface of microglia cells found in senile plaques in Alzheimer's diseases patients. *See* Xia *et al.*, "Chemokines/Chemokine Receptors in the Central Nervous System and Alzheimer's Disease," *J. Neurovirology*, Vol. 5, pp. 32-41 (1999) ("Xia II", copy provided with the enclosed Information Disclosure Statement). Xia I teaches that CCR3 and its chemokine ligands are associated with inflammatory responses, and that because the inflammatory response has been implicated in the pathogenesis of Alzheimer's disease, CCR3 may be associated with that disease specifically. (Xia I, pages 31 and 36). Indeed, Xia I teaches that brain tissue taken from a patient having Alzheimer's disease shows an over-expression of CCR3. (*Id.*). Xia II teaches that the activation of CCR3 and other chemokine receptors in the Alzheimer's disease brain may play a role in the disease and therefore have potential as therapeutic targets for the treatment of Alzheimer's disease. (Xia II, pages 35 and 38). For these reasons, one of ordinary skill in the art, reading the instant specification and Xia I and Xia II, would expect that the compounds of the instant claims, which inhibit CCR3, would be useful in treating Alzheimer's disease. Therefore, claims 11 and 15, to the extent that they teach the treatment of Alzheimer's disease, are enabled.

4. The predictability in the art.

While it may be generally true that the pharmaceutical arts are often unpredictable, Applicants note that the present disclosure establishes, *inter alia*, that CCR3 is known to be related through its role in the regulation of eosinophils to the diseases and disorders of the instant claims. (*See* pages 1-3 of the specification). Furthermore, the relationship between CCR3 and the diseases and disorders of claims 10-11 and 13-15 has been demonstrated above to be generally known in the art. (*See, e.g.*, specification, page 1 and White, page 36626).

The references cited above further support this conclusion by providing experimental data supporting the connection between CCR3 and the specific diseases and disorders of claims 10-11 and 13-15. Because there is an established correlation between CCR3 and the diseases and disorders of claims 10-11 and 13-15, Applicants submit that there is significant predictability in the art for the use of CCR3 antagonists to treat these diseases and disorders.

5. The relative skill/level of skill in the art.

The Examiner alleges that those of "relative skill in the art level are those with the level of skill of the authors of the references cited to support the Examiner's position." (Office Action, page 4). The Examiner further alleges that those persons skilled in the art have advanced degrees and experience in "therapeutic methods for treating disorders related to CCR3 receptors." (*Id.*). Applicants point out that, to the extent persons skilled in the art are experienced in "therapeutic methods for treating disorders related to CCR3 receptors," the relative level of skill in the art is high because the references cited above demonstrate that CCR3 receptors and the diseases and disorders of the instant claims were well known to be related at the time of the invention. In other words, the references cited above established a relationship between the CCR3 receptor and the diseases of the instant claims, and that this relationship would have been recognized by those of ordinary skill in the art at the time of the invention.

6., 7. The amount of direction or guidance presented and working examples.

The specification provides many examples of compounds within the scope of the instant claims having CCR3 antagonistic activity. Further, the specification provides detailed experimental procedures for testing additional compounds for CCR3 activity. These examples, coupled with the knowledge that the antagonism of CCR3 is associated with the diseases and disorders of claims 10-11 and 13-15, provide one of ordinary skill in the art significant guidance to practice the claimed invention. Even in unpredictable arts, a disclosure of every operable species is not required to satisfy enablement. *See* MPEP § 2164.03.

The Examiner alleges that the specification does not provide guidance for the treatment and prevention of a disease related to CCR3, and the prevention of asthma. Applicants point out that the presently amended claims do not recite methods of treating or preventing "a disease related to CCR3," nor do they recite methods of preventing diseases. The instant claims recited specific classes of diseases and disorders shown to be associated

with the CCR3 receptor. Furthermore, it is the Examiner's burden to provide evidence of non-enablement. *Wands*, 8 U.S.P.Q.2d at 1404. Thus, because the Examiner has not presented evidence to the contrary, the instant disclosure provides one of ordinary skill in the art with ample guidance, including specific examples, to practice the claimed invention.

8. The quantity of experimentation necessary.

The Examiner alleges that one of ordinary skill in the art would be "burdened with undue experimentation to practice the invention" because of the "state of the art as discussed by the references above," the "high unpredictability in the art" and the "lack of guidance provided in the specification." (Office Action, page 4). Applicants disagree. First, Applicants point out that mere routine experimentation is not undue. *See Wands*, 8 U.S.P.Q.2d at 1404. As shown above, the connection between CCR3 antagonism and the diseases and disorders recited in claims 10-11 and 13-15 is well established in the art. Thus, only routine experiments evaluating the CCR3 antagonistic activity of the claimed compounds are necessary to enable the compositions and methods of the instant claims. The instant disclosure provides detailed methods of *in vitro* screening, methods which were used to evaluate the compounds of the instant claims for CCR3 activity. (*See* pages 33-39 of the specification). Indeed, as discussed above, many compounds of the instant claims were shown to be CCR3 antagonists. Additional *in vitro* and *in vivo* models are known in the art for evaluating activity against the diseases and disorders of the instant claims. For example, Xia I teaches an *in vitro* brain tissue screen for CCR3 in Alzheimer's disease studies. (Xia I, page 32). Following these examples, one of ordinary skill in the art need only use conventional medical and pharmacological techniques to prepare compounds of the instant claims for treating the diseases and disorders of claims 10-11 and 13-15. One skilled in the art could select a compound of the instant claims having CCR3 antagonistic activity, further screen the compound using an *in vitro* or *in vivo* test for the specific disease known in the art, prepare a pharmaceutical composition of the compound, and administer the composition to a patient having a disease or disorder known to be associated with CCR3. Thus, in view of the teachings of the instant disclosure, Applicants submit that it would require a minimal amount of routine work to use the compounds of the present invention to treat a patient having any of the claimed diseases or disorders. To the extent that the Examiner alleges that the "state of the art" and the "high unpredictability in the art" require undue experimentation, Applicants point out that these factors, as discussed above, support the enablement of the instant claims

because of the well-established relationship between the CCR3 receptor and the diseases and disorders of the instant claims.

Therefore, considering each the above factors, the Examiner has not put forth sufficient evidence demonstrating a lack of enablement. Applicants respectfully request that the rejection be withdrawn.

Conclusion

No fees are believed due in connection with this Response. However, pursuant to 37 C.F.R. § 1.136(a)(3), the Commissioner is authorized to charge all required fees, fees under 37 C.F.R. § 1.17, and all required extension of time fees, or credit any overpayment, to Jones Day, U.S. Deposit Account No. 503013 (referencing 191354-999004).

If the Examiner believes it would be useful to advance prosecution, the Examiner is invited to telephone the undersigned at (858) 314-1200.

Respectfully submitted,

Date: 11/13/08

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